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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

HUFF, SHEELA JITENDRA

ART UNIT PAPER NUMBER

1642

DATE MAILED: 04/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

08/716,531

Applicant(s)

MAHE ET AL.

Examiner

Sheela J Huff

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-11 and 16-19 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-11 and 16-19 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)                      4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_.
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)                      5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_.
- 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

Prosecution is hereby re-opened.

Claims 1-11 and 16-19 are pending.

All outstanding rejections are withdrawn.

### ***New Grounds of Rejection***

#### ***Claim Objections***

Claim 3 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. This rejection is made in view of the Board Decision, mailed 8/15/02.

Claim 3 does not further limit claim 1 because claim 3 merely states that the proline must be in D form and this is already stated in claim 1.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Oluyomi et al. European Journal of Pharmacology vol. 258 p. 131 (1991) or Ferreira et al US 5389615 as evidenced by applicant's admission on page 1 of the specification, Stedman's Medical Dictionary, 24<sup>th</sup> edition (1989) p. 707-708 and 1218 and Oxford Medical Companion, ed. J. Walton, J. Barondess and S. Lock (1994) p. 969.

The claims are directed to a method of treating inflammation by administering a therapeutically effective amount of lysine-D-proline-valine. On page 1 of the specification, applicant defines inflammation in terms of swelling, pain, redness and warmth. Stedman's corroborates this by defining inflammation in the same terms (i.e. swelling, pain, redness and warmth) (see page 707-708 of Stedman's). The state of the art defines "treatment" as "the application of remedies to disease; the general management of illness" and "to cure sometimes, to relieve often, to comfort always" (see Oxford p. 969) and the state of the art defines "relieve" as "to free wholly or partly from pain or discomfort" (Stedman's p. 1218). Taken together, treatment is defined as the general management of illness by providing relief using remedies. The relief can be either whole or **partial**. Since there are four characteristic symptoms (swelling, pain, redness and warmth) of inflammation, treatment of inflammation reads on the partial relief of inflammation and this reads on treating at least one symptom.

Oluyomi et al disclose the use of the K(D)PV and biological equivalents thereof in pharmaceutically acceptable formulations to treat inflammatory pain ( abstract, p. 134-135 and Tables 2-3). The reference further states that the peptide analogs containing the dipeptide lys-pro "constitute a novel approach to the control of pain, particularly **inflammatory** pain "(emphasis added, p. 131 second column, first full paragraph). The reference states that the peptide inhibits the release of prostaglandin and other inflammatory agents (p. 136, first column, lines 5-9 from the bottom) and additionally on

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page 137, first column, lines 8-11 that "this confirms the peripheral anti-inflammatory activity of this peptide" (this peptide refers to lys-D-pro-val). In view of the state of the art definitions, the reference is dealing with the treatment of inflammation.

Ferreira et al disclose the use of tripeptides as medicaments to treat or prevent pain wherein said tripeptides are of the formula X-Pro-Y (formula I) where X can be lys or arg and Y can be any amino acid (col. 1, lines 30-50) where the preferred compounds are X=lys or D-lys (col. 2, line 22) and Y=valine (col. 2, line 31) and each of these amino acids can be in its D-form (col. 2, lines 13-17). The preferred form of pro is also D (col. 2, lines 15-17). These compounds read on the tripeptides and functional equivalents thereof of claims 1-3. In view of the state of the art definitions, the reference is dealing with the treatment of inflammation.

01/02  
Claims 1-3 and 5-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Hiltz et al Peptides vol. 12 p. 767 (1991). This rejection is made in view of the Board Decision, mailed 8/15/02.

Hiltz et al disclose the tripeptide lysine-proline-valine, where the proline is in its D form (see Table 1, p. 768 third listed peptide). This peptide was tested for anti-inflammatory activity by administering 10ug ( $2.6 \times 10^{-8}$  M), 20ug ( $5.2 \times 10^{-8}$  M), 40ug ( $1.04 \times 10^{-7}$  M) and 80ug ( $2.08 \times 10^{-7}$  M) in 0.2 ml of sterile saline (p. 768-769). These amounts read on "anti-inflammatory effective amount" as recited in claim 1 and reads on the concentration ranging from  $10^{-21}$  M to  $10^{-3}$  M (see specification page 6, lines 14-21). As disclosed in Table 1, Hiltz et al show, in numerical terms, the anti-inflammatory activity of the tripeptide. It is noted that Hiltz et al state that their tripeptide has no

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significant anti-inflammatory activity. The reference states that the results were unsatisfactory. Applicant is directed to Ex Parte Thurman, 132 USPQ 66, 67-68 (Bd. App. 1960) which states that if applicant's claims read directly on what is disclosed in the prior art, such claims cannot be allowed even though the prior art teaches unsatisfactory results whereas the applicant demonstrates successful results. It is elementary that the applicant's claims must define something specifically different from what is explicitly taught by the prior art and the change must not be an obvious one. Applicant is also directed to Celeritas Technologies Ltd. V. Rockwell International Corp., 150 F.3<sup>rd</sup> 1354, 1361, 47 USPQ2d 1516, 1522 (Fed. Cir. 1998) (A reference is no less anticipatory if after disclosing invention, the reference then disparages it. Thus, the question whether a reference "teaches away" from the invention is inapplicable to an anticipation analysis). Applicant's are also directed to In re Woodruff, 919 F.2d 1575, 1578, 16 USPQ2d 1934, 1936 (Fed. Cir 1990) (It is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable).

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1-24 awarded  
Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over

Ferreira et al US 5389615 in view of applicant's admission on page 1 of the specification, Stedman's Medical Dictionary, 24<sup>th</sup> edition (1989) p. 707-708 and 1218 and Oxford Medical Companion, ed. J. Walton, J. Barondess and S. Lock (1994) p. 969.

Ferreira et al disclose the use of tripeptides as medicaments to treat or prevent pain wherein said tripeptides are of the formula X-Pro-Y (formula I) where X can be lys or arg and Y can be any amino acid (col. 1, lines 30-50) where the preferred compounds are X=lys or D-lys (col. 2, line 22) and Y=valine (col. 2, line 31) and each of these amino acids can be in its D-form (col. 2, lines 13-17). The preferred form of pro is also D (col. 2, lines 15-17). These compounds read on the tripeptides and functional equivalents thereof of claims 1-4.

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add 014

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The only difference between the prior art and the reference, if any, is that the reference deals with the treatment of one facet of inflammation (ie pain) and not all four facets of inflammation (ie swelling, pain, redness and warmth). The only other difference between that and the instant invention is the specific use of D-lys-Dpro-Dval (claim 4) and the combination of another known anti-inflammatory agent with the tripeptides.

As discussed above, the reference clearly suggests the making and the use of Dlys-Dpro-Dval (preferred embodiment). Therefore, in view of this suggestion, it would have been obvious to one of ordinary skill in the art at the time of the invention to make and use D-lys-Dpro-Dval to treat pain. The combination of two or more known agents to treat a disease is within the purview of one skilled in the art. Dosages are within the purview of one skilled in the art. Furthermore, on page 1 of the specification, applicant defines inflammation in terms of swelling, pain, redness and warmth. Stedman's corroborates this by defining inflammation in the same terms (see page 707-708 of Stedman's). The state of the art defines "treatment" as "the application of remedies to disease; the general management of illness" and "to cure sometimes, to relieve often, to comfort always" (see Oxford p. 969) and the state of the art defines "relieve" as "to free wholly or partly from pain or discomfort" (Stedman's p. 1218). Taken together, treatment is defined as the general management of illness by providing relief using remedies. The relief can be either whole or **partial**. Since there are four characteristic symptoms (swelling, pain, redness and warmth) of inflammation, treatment of inflammation reads on the partial relief of inflammation and this reads on treating at



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least one symptom. Therefore, in view of the state of the art definition of "treatment", it would have been obvious to one of ordinary skill in the art at the time of applicant's invention that the Ferreira et al peptide be used to treat inflammation.

*Keep*  
Claims <sup>1-2, 4-6</sup> ~~1-6~~ and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ferreira et al US 5389615, applicant's admission on page 1 of the specification, Stedman's Medical Dictionary, 24<sup>th</sup> edition (1989) p. 707-708 and 1218 and Oxford Medical Companion, ed. J. Walton, J. Barondess and S. Lock (1994) p. 969 in view of Lipton US 5157023 and Oluyomi et al. European Journal of Pharmacology vol. 258 p. 131 (1991). *add 11*

The primary references and the combination of the primary references have been discussed above.

The only difference between that and the instant invention is the use of protecting groups.

Lipton disclose the use of protected peptides (specifically acetyl-KPV) and that the use of protected peptides is preferred because the protection group can confer stability to the peptide by decreasing the problems of enzymatic attack and degradation and also discloses that the protected tripeptide is more active than the unprotected form (col. 4, lines 58-68).

Therefore, in view of the enhanced activity of the protected peptide over the unprotected peptide, it would have been obvious to one of ordinary skill in the art at the time of the invention to use a protecting groups, such as acetyl, to protect the tripeptides

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of the primary reference to confer stability to the tripeptides. It is noted that the tripeptides of the primary and secondary references are related (see Oluyomi et al p. 131 which discloses that amino acids 193-195 of IL-1beta are KPV and that amino acids 11-13 of alpha MSH are KPV and that these peptides are related).

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Claims <sup>1-2, 4-11</sup> ~~1-11~~ and ~~16-18~~ <sup>20</sup> are rejected under 35 U.S.C. 103(a) as being unpatentable over Ferreira et al US 5389615, applicant's admission on page 1 of the specification, Stedman's Medical Dictionary, 24<sup>th</sup> edition (1989) p. 707-708 and 1218 and Oxford Medical Companion, ed. J. Walton, J. Barondess and S. Lock (1994) p. 969 in view of Nordlund et al US 4874744, Lipton US 5157023 and Remington's Pharmaceutical Science Ch 87 and 92 and Oluyomi et al. European Journal of Pharmacology vol. 258 p. 131 (1991). <sup>add 11</sup>

The primary references and the combination thereof have been discussed above.


The only difference between the instant invention and the reference is (1) the use of the tripeptide in a topical formulation, (2) the use of a protecting group, (3) the specific mention of Dlys-Dpro-Dval and (4) the combination of another known anti-inflammatory agent with the tripeptides.

As discussed above, the primary reference clearly suggests the making and use of D-lys-Dpro-Dval (preferred embodiment).

Lipton disclose the use of protected peptides (specifically acetyl-KPV) and that the use of protected peptides is preferred because the protection group can confer stability to the peptide by decreasing the problems of enzymatic attack and degradation and also discloses that the protected tripeptide is more active than the unprotected form (col.. 4, lines 58-68).

Nordlund discloses that alpha MSH can be applied topically to treat inflammatory skin diseases such as dermatitis in a concentration of 10-2M/cm<sup>2</sup> to 10-10M.cms (abstract, col. 1, lines 5-41, summary of the invention, col. 2, lines 33-65). The pharmaceutical formulation includes ointments and creams (col.. 2, lines 50-55). Remington's is cited to show that formulation of topical treatments and aerosols is well known in the art.

Therefore, in view of the suggestion of the primary reference to make and use D-lys-D-pro-D-val, it would have been obvious to one of ordinary skill in the art at the time of the invention to make and use D-lys-D-pro-Dval to treat pain. It also would have been obvious to one of ordinary skill in the art to use a protecting groups, such as acetyl, to protect the tripeptides of the primary reference to confer stability to the tripeptides. It is noted that the tripeptides of the primary reference and secondary references are both derived from amino acids 11-13 of alpha MSH. It also would have been obvious to use the tripeptides of the primary reference to treat inflammatory disorders of the skin and to make formulations suitable for topical administration because according to Nordlund et al MSH is used to treat such disorders and the tripeptides of the primary reference are amino acids 11-13 of MSH (see Oluyomi et al p. 131 which discloses that amino acids 193-195 of Il-1beta and that amino acids 11-13 of alpha MSH are KPV and that these peptides are related). The combination of two or more known agents to treat a disease is within the purview of one skilled in the art. Dosages are within the purview of one skilled in the art.

 Claims 1-3, 5-11 and 16-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oluyomi et al European Journal of Pharmacology vol. 258 p. 131 (1991), applicant's admission on page 1 of the specification, Stedman's Medical

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Dictionary, 24<sup>th</sup> edition (1989) p. 707-708 and 1218 and Oxford Medical Companion, ed. J. Walton, J. Barondess and S. Lock (1994) p. 969 in view of Nordlund et al US 4874744, Lipton US 5157023 and Remington's Pharmaceutical Science Ch 87 and 92.

The primary references and the combination thereof have been discussed above.

The only difference between the instant invention and the reference is (1) the use of the tripeptide in a topical formulation, (2) the use of a protecting group and (3) the combination of another known anti-inflammatory agent with the tripeptides.

Lipton discloses the use of protected peptides (specifically acetyl-KPV) and that the use of protected peptides is preferred because the protection group can confer stability to the peptide by decreasing the problems of enzymatic attack and degradation and also discloses that the protected tripeptide is more active than the unprotected form (col. 4, lines 58-68).

Nordlund discloses that alpha MSH can be applied topically to treat inflammatory skin diseases such as dermatitis in a concentration of 10<sup>-2</sup>M/cm<sup>2</sup> to 10<sup>-10</sup>M/cm<sup>2</sup> (abstract, col. 1, lines 5-41, summary of the invention, col. 2, lines 33-65). The pharmaceutical formulation includes ointments and creams (col. 2, lines 50-55). Remington's is cited to show that formulation of topical treatments and aerosols is well known in the art.

In view of Lipton, it would have been obvious to one of ordinary skill in the art at the time of the invention to use a protecting group, such as acetyl, to protect the tripeptides of the primary reference to confer stability. It is noted that the tripeptides of the primary reference and secondary references are related. It also would have been obvious to use the tripeptides of the primary reference to treat inflammatory disorders of the skin and to make formulations suitable for topical administration because according to Nordlund et al MSH is used to treat such disorders and the tripeptides of the primary

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reference are amino acids 11-13 of MSH. The combination of two or more known agents to treat a disease is within the purview of one skilled in the art. Dosages are within the purview of one skilled in the art.

Claims 1-11 and 16-19 are rejected under 35 U.S.C. 103 as being unpatentable over Hiltz et al Peptides vol. 12 p. 767 (1991) in view of Nordlund et al US 4874744, Lipton US 5157023 and Remington's Pharmaceutical Science Ch 87 and 92. This rejection is made in view of Board Decision, mailed 8/15/02.

The primary reference has been discussed above.

The only difference between the instant invention and the reference is (1) the use of the tripeptide in a topical formulation, (2) the use of a protecting group and (3) the combination of another known anti-inflammatory agent with the tripeptides.

Lipton disclose the use of protected peptides (specifically acetyl-KPV) and that the use of protected peptides is preferred because the protection group can confer stability to the peptide by decreasing the problems of enzymatic attack and degradation and also discloses that the protected tripeptide is more active than the unprotected form (col.. 4, lines 58-68).

Nordlund discloses that alpha MSH can be applied topically to treat inflammatory skin diseases such as dermatitis in a concentration of 10<sup>-2</sup>M/cm<sup>2</sup> to 10<sup>-10</sup>M.cms (abstract, col. 1, lines 5-41, summary of the invention, col. 2, lines 33-65). The pharmaceutical formulation includes ointments and creams (col.. 2, lines 50-55). Remington's is cited to show that formulation of topical treatments and aerosols is well known in the art.

In view of Lipton, it would have been obvious to one of ordinary skill in the art at the time of the invention to use a protecting group, such as acetyl, to protect the

tripeptides of the primary reference to confer stability. It is noted that the tripeptides of the primary reference and secondary references are related. It also would have been obvious to use the tripeptides of the primary reference to treat inflammatory disorders of the skin and to make formulations suitable for topical administration because according to Nordlund et al MSH is used to treat such disorders and the tripeptides of the primary reference are amino acids 11-13 of MSH. The combination of two or more known agents to treat a disease is within the purview of one skilled in the art.

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheela J Huff whose telephone number is 703-305-7866. The examiner can normally be reached on T,Th 6am-12pm and alternate Mondays 6am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

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*S.J.H.*

*Sheela J. Huff*

Sheela J Huff  
Primary Examiner  
Art Unit 1642

sjh  
April 10, 2003

*Jasemine C. Chambers*

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